Sustained Therapeutic Exposure With Once-Daily Oral Deucrictibant XR Tablet for Prophylaxis of Hereditary Angioedema Attacks: Results of a Pharmacokinetics Study in Healthy Volunteers

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Key takeaways

Results of this Phase 1 pharmacokinetic study in healthy volunteers support the once-daily administration in Phase 3 trials investigating the efficacy and safety of deucrictibant extended-release (XR) tablet for prophylaxis of bradykinin-mediated angioedema attacks.

Safety

Deucrictibant XR tablet was well tolerated with no treatment-related TEAEs

Pharmacokinetic profile

Sustained exposure through ≥24 hours supports once-daily dosing for HAE attack prevention

4-fold

higher mean plasma concentration at 24 hours than the estimated threshold concentration for therapeutic exposure with a single dose of deucrictibant XR tablet

HAE, hereditary angioedema; TEAE, treatment-emergent adverse event; XR, extended-release.

Background

- **Hereditary angioedema (HAE):** a rare genetic condition characterized by painful and often disabling swelling attacks that affect the skin, gastrointestinal tract, and upper airways.[1-3]
- **Deucrictibant:** a selective, orally administered bradykinin B2 receptor antagonist under development for prophylactic and on-demand treatment of HAE attacks.[4-13]
- **Clinical trials:** deucrictibant was efficacious and generally well tolerated when evaluated in Phase 2 clinical trials for prophylactic (CHAPTER-1, NCT05047185) and on-demand (RAPIDe-1, NCT04618211) treatment of HAE attacks.[6,9,10,13]
- **Deucrictibant extended-release (XR) tablet:** in the prophylaxis CHAPTER-1 trial, deucrictibant was administered as immediate-release (IR) capsule formulation, dosed twice daily, as a proof-of-concept for the once-daily deucrictibant XR tablet, which is the intended commercial formulation of deucrictibant for prophylactic HAE treatment.[14]

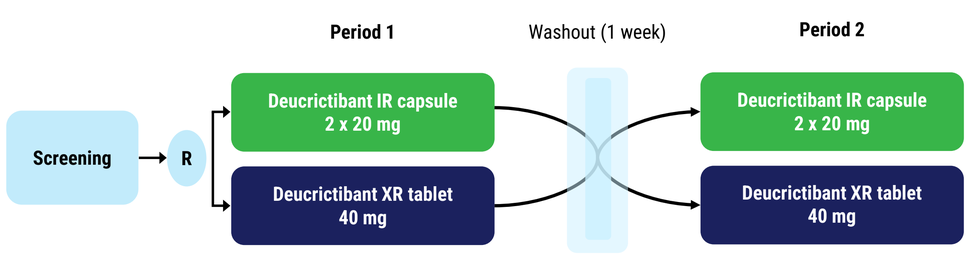
Objective

Characterize the single-dose pharmacokinetics of deucrictibant XR tablet (40 mg) and deucrictibant IR capsule (2 x 20 mg) in healthy volunteers in a Phase 1, open-label, randomized, 2-period, crossover study (PHA022121-C020*).

Methods

- **Participants:** healthy volunteers received, in randomized order, a single oral dose of deucrictibant XR tablet (40 mg) or deucrictibant IR capsule (2 x 20 mg taken simultaneously) under fasting conditions.

Figure 1. PHA022121-CO20 study design



IR, immediate-release; R, randomization; XR, extended-release.

- **Primary objective:** characterization of single-dose pharmacokinetics (PK) of both formulations.
- **Secondary objectives:** included assessment of relative bioavailability, safety, and tolerability.
  - Plasma concentrations of deucrictibant were determined during each treatment period at pre-dose and over a 48-hour evaluation period after dosing on day 1.
  - PK analyses were performed on the plasma concentration-time data of each participant.
- **Safety and tolerability:** assessed throughout the study until end-of-study visit, which took place between 5 to 9 days after the last treatment-defined assessment (or after early withdrawal).
- **Statistical analyses:** statistical analyses were calculated for the PK parameters of deucrictibant and its metabolites. Statistics included sample size, mean, median, minimum, maximum, standard deviation, percent coefficient of variation, and geometric mean.

Results

Patient population

- A total of 15 participants were included in the study; one person who received deucrictibant IR capsule in period 1 discontinued 4 hours post-dose due to problems with blood sample withdrawal.
- This analysis included 14 participants with evaluable PK data for both formulations.

PK data

Table 1. Summary of PK characteristics

PK parameter	Deucrictibant XR tablet (N=14[a])	Deucrictibant IR capsule (N=14[b])
C_{max}, ng/mL	87.2 (25.5)	547 (193)
t_{max}, hours, median (range)	5.03 (3.98–24.00)	1.00 (0.50–1.50)
C_{12h}, ng/mL	47.3 (27.7)	31.1 (19.9)
C_{24h}, ng/mL	51.6 (29.7)	7.47 (6.88)
AUC_{12h}, ng·h/mL	571 (188)	1509 (527)
AUC_{24h}, ng·h/mL	1124 (416)	1703 (660)
AUC_{last}, ng·h/mL	1609 (668)	1794 (742)
AUC_{inf}, ng·h/mL	1547 (699)	1799 (745)
t_{last}, hours, median (range)	47.64 (47.25–48.00)	47.55 (23.98–48.00)
$t_{1/2}$, hours	5.72 (1.70)	5.10 (1.28)
CL/F, L/hours	31.5 (14.7)	26.5 (12.7)
V_z/F, L	245 (129)	179 (52.1)

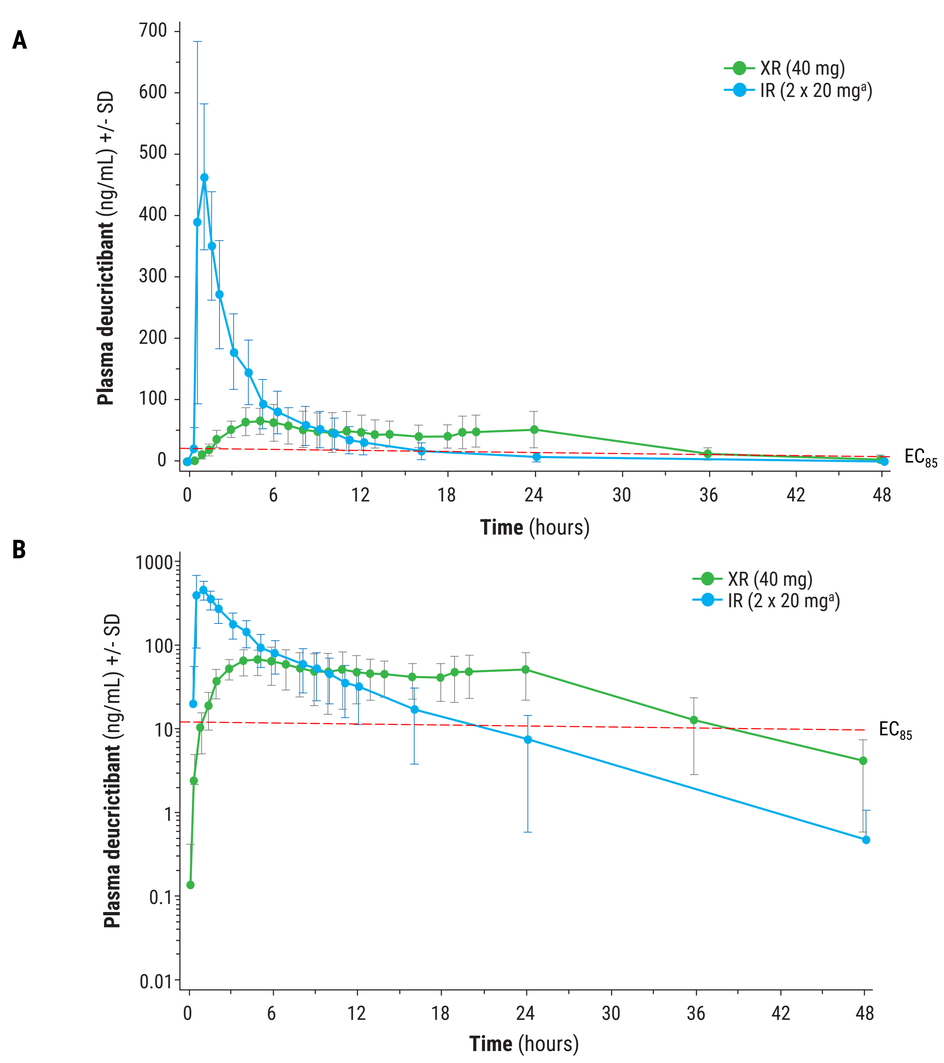
Mean ± standard deviation unless otherwise noted. AUC_{xh}, area under the concentration-time curve from time of drug administration to x hours; AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve to the last measurable plasma concentration; CL/F, oral clearance; C_{max}, maximum plasma concentration; C_{12h}, plasma concentration at 12 hours post-dose; C_{24h}, plasma concentration at 24 hours post-dose; IR, immediate-release; L, liter; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; t_{last}, time of last measurable concentration; t_{max}, actual sampling time to reach the maximum observed analyte concentration; V_z/F, volume of distribution during the terminal phase; XR, extended-release. [a]n=12 for AUC_{inf}, $t_{1/2}$, V_z/F, and CL/F. [b]n=15 for C_{max} and t_{max}.

Results

Mean plasma concentration

- Mean plasma concentration at 24 hours post-dose (C_{24h}) of deucrictibant XR was approximately 4-fold higher than the effective concentration estimated to provide 85% maximal response (EC_{85}; 13.8 ng/mL).
  - C_{24h} of deucrictibant XR was higher than EC_{85} in 12/14 participants and higher than the effective concentration estimated to provide 50% maximal response (EC_{50}; 2.4 ng/mL) in all participants.
- Deucrictibant XR resulted in a sustained level in circulation exceeding the EC_{85} therapeutic threshold from ~1.5 to at least 24 hours post-dose.
  - Deucrictibant XR resulted in a steady rise in mean plasma concentration to a maximum at 5 hours post-dose; the mean plasma concentration remained relatively stable between 4 and 24 hours post-dose.
  - Deucrictibant IR resulted in a mean plasma concentration exceeding EC_{85} within 15-30 minutes.

Figure 2. (A) Linear and (B) semi-logarithmic plasma concentration-time profiles



EC85, concentration estimated to provide 85% maximal response; IR, immediate-release; SD, standard deviation; XR, extended-release. Error bars represent standard deviation. n = number of participants in each group.
[a]Single oral dose of 2 x 20 mg deucrictibant IR capsule.

Relative bioavailability and overall exposure

Table 2. Geometric least square means

PK parameter[a]	Deucrictibant XR tablet (N=14[a])	Deucrictibant IR capsule (N=14[b])	LS means ratio, %	90% confidence intervals
C_{max}, ng/mL	86.2	513	16.82	14.86–19.05
AUC_{12h}, ng·h/mL	546	1420	38.46	33.75–43.82
AUC_{24h}, ng·h/mL	1057	1583	66.77	56.78–78.53
AUC_{last}, ng·h/mL	1470	1650	89.08	73.30–108.27
AUC_{inf}, ng·h/mL	1438	1655	86.90	69.17–109.17

AUC_{xh}, area under the concentration-time curve from time of drug administration to x hours; AUC_{inf}, area under the plasma concentration-time curve extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve to the last measurable plasma concentration; C_{max}, maximum plasma concentration; h, hours; IR, immediate-release; L, liter; LS, least squares; PK, pharmacokinetic; XR, extended-release. [a]n=12 for AUC_{inf}. [b]n=15 for C_{max}.

- Geometric least square mean ratios of AUC_{last} showed that relative bioavailability and overall exposure of the two formulations were comparable.
- Deucrictibant XR tablet compared with deucrictibant IR capsule showed:
  - 83% lower mean values for C_{max} (86.2 vs. 513 ng/mL)
  - a longer median t_{max} (1 vs 5.03 hours).
- Mean $t_{1/2}$ of deucrictibant was comparable for the XR tablet and IR soft capsules: 5.72 and 5.10 hours, respectively.

Safety

- No treatment-related treatment-emergent adverse events (TEAEs) reported.
- Four TEAEs were reported, all of which were mild.
  - A single occurrence of dizziness, headache, urinary tract infection, and viral infection were reported.
- No serious TEAEs or TEAEs leading to drug withdrawal or study discontinuation were reported.

This presentation includes data for an investigational product not yet approved by regulatory authorities.

References

1. Busse PJ, et al. *N Engl J Med*. 2020;382:1136-48. **2.** Banerji A, et al. *Ann Allergy Asthma Immunol*. 2020;124:600-7. **3.** Betschel SD, et al. *J Allergy Clin Immunol Pract*. 2023;11:2315-25. **4.** Lesage A, et al. *Front Pharmacol*. 2020;11:916. **5.** Lesage A, et al. *Int Immunopharmacol*. 2022;105:108523. **6.** RAPIDe-1 https://www.clinicaltrials.gov/study/NCT04618211. Accessed May 20, 2025. **7.** RAPIDe-2. https://www.clinicaltrials.gov/study/NCT05396105. Accessed May 20, 2025. **8.** RAPIDe-3. https://clinicaltrials.gov/study/NCT06343779. Accessed May 20, 2025. **9.** Maurer M, et al. Presented at: AAAAI; February 24–27, 2023; San Antonio, TX, USA. **10.** CHAPTER-1. https://www.clinicaltrials.gov/study/NCT05047185. Accessed May 20, 2025. **11.** CHAPTER-3. https://clinicaltrials.gov/study/NCT06669754. Accessed May 20, 2025. **12.** CHAPTER-4. https://clinicaltrials.gov/study/NCT06679881. Accessed May 20, 2025. **13.** Aygören-Pürsün, et al. Presented at: EAACI; May 31–June 3, 2024; Valencia, Spain. **14.** Groen K, et al. Presented at: ACAAI 2022. November 10–14, 2022; Louisville, KY, USA.

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